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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|-------------|----------------------|---------------------|------------------|
| 09/831,182 | 07/18/2001 | Stefano Colloca | B-4175PCT 61 | 1087 |
| 7590 | 05/05/2004 | | EXAMINER | |
| MERCK & CO., INC. 126 E. LINCOLN AVENUE P. O. BOX 2000 RAHWAY, NJ 07065-0907 | | | WINKLER, ULRIKE | |
| | | ART UNIT | PAPER NUMBER | |
| | | 1648 | | |
| DATE MAILED: 05/05/2004 | | | | |

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | |
|------------------------------|------------------------|---------------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 09/831,182 | COLLOCA, STEFANO |
| Examiner | Art Unit | |
| Ulrike Winkler | 1648 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM

THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 23 December 2003.
 2a) This action is **FINAL**. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-21 and 24-26 is/are pending in the application.
 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 1-21 and 24-26 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
 Paper No(s)/Mail Date July 13, 2003.

- 4) Interview Summary (PTO-413)
 Paper No(s)/Mail Date. _____.
 5) Notice of Informal Patent Application (PTO-152)
 6) Other: _____.

DETAILED ACTION

The Amendment filed December 23, 2003 in response to the Office Action of September 24, 2003 is acknowledged and has been entered. Claims 1-21 and 24-26 are pending and are currently being examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on July 14, 2002 (Paper No.22), was received by the technology center in September 2003.

Claim Rejections - 35 USC § 112

The rejection of claims 1-21 and 24-26 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention **is withdrawn**. Applicant's have indicate that "defective" refers to an adenovirus genome that has been modified such that it is incapable, by itself, of either replication of viral DNA and/or encapsidation.

The rejection of claims 1 and 18-21 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention **is maintained**. In claims 18-21 the term "totally or partially constituted" in not clear, how much is derived from a human adenovirus and how much may

derived from other viral genic units? The metes and bound of what is encompassed by the term in not clear because one of ordinary skill in the art would not know how much of one viral genic unit is needed. Applicant's arguments are that the claims "are not indefinite in recitation of the phrase "totally or partially constituted" because one of ordinary skill in the art could readily appreciate how much of either the first or second genic unit could be comprised of sequences from a single adenovirus species (e.g., human adenovirus sequences)." The argument goes on to say that the function of the encoded product is more important. Claims 18-21 depends from claim 1, which already splits the adenovirus onto two different genetic units were the second unit comprises at least one unit not found in the first genetic unit. Claims 18-21 require the addition of a human adenovirus where the adenovirus "totally or partially constitute" presumably the activity of the first genetic unit, however, the claim is not clear if the human adenovirus includes or excludes a complete human adenovirus for the purpose of "totally or partially constituted".

The rejection of claims 1-21 and 24-26 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using human adenoviral vectors and cell lines expressing human adenoviral constructs, does not reasonably provide enablement for adenoviruses derived from other species. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims **is maintained** for reasons of record.

Applicant's arguments are that one of skill in the art "could readily identify those components required for replication and/or particle assembly by deleting regions in a chosen

wild-type adenovirus genome and determining whether proper replication and/or virion assembly occurs without providing said deleted regions in trans". Applicant arguments goes on to state that the genomes of alternate species where known at the time of the invention citing table 1 of Davison, A.J.

It remains the Offices position that it could not be predicted that a deleted human adenovirus can be complemented with a swine, duck, goat, canine or camel adenovirus sequences. Or that a deleted goat adenovirus can be complemented with duck adenoviral sequences. A review of the literature indicated that the only adenovirus complementation assays disclosed involved the replacement the capsid region from one human adenovirus with the capsid region of another human adenovirus. This type of change altered the type of cell that could be infected by the adenovirus. The human adenosines are closely linked genetically. The claims are drawn to a cell line for the production of helper dependent adenovirus vector, were the cell line provides the complementing factor needed to package the defective helper dependent vector. The claims are not limited to human adenoviruses and can include all animal viruses. The state of the prior art, indicates that there are significant differences between human adenoviruses (HAV) and porcine adenoviruses 3 (PAV3), because of these differences there is no reasonable expectation of success in applying the teaching of the instant specification which is drawn to human adenoviruses and apply them to porcine or bovine adenoviruses. PAV3 is very different to the human adenovirus at the genome (genic) level only approximately 54 % identity between PAV3 and HAV2 and HAV5 exists at the DNA level (see Gene Bank Accession #J01917, M73260 and AF083132). At the protein level the comparisons also show a significant difference. The PAV3 fiber protein has only 23.5 % identity with the HAV fiber protein, the

PAV3 penton protein has about 58% identity with the HAV penton protein. These differences clearly show that PAV3 is very different to HAV in both genetic and protein sequence content. The mere relationship of being in the same virus family or sharing the sharing of structural and function features does not provide one skilled in the art with the ability to manipulate a comparable sequence at the molecular level, to predict with reasonable success the structure and function of expressed proteins. (Tuboly et al. Restriction endonuclease analysis and physical mapping of the genome of porcine adenovirus type 5. Virus Research. 1995, Vol. 37, No. 1, pages 49-54). Davison (Journal of General Virology cite in applicants response, figure 1) indicates that adenovirus from different species are structurally very different, figure 1 provides a phylogeny tree that shows the structural difference among the hexon protein of the various adenoviruses. The structure of a molecule tends to be linked to the function, therefore, with large structural differences among the species there is no predictability that one structure can be replace another structure.

There is no working example provided by the inventor demonstrating that the claimed cell line construction would be effective at packaging adenoviral vector from other species. Due to the breadth of the claims encompassing all adenoviruses, the inability of the skilled artisan to a priori predict how to make the appropriate constructs for example in PAV3, the lack of direction provided by the inventor, and the lack of working examples, it is determined that an undue quantity of experimentation would be required for one skilled in the art to use the invention in its full scope.

Conclusion

No claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for informal communications use 703-308-4426.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.


ULRIKE WINKLER, PH.D.
PATENT EXAMINER

5/3/04